Risk Factors Associated with Heterotopic Ossification Diagnoses in Recent Combat Amputees

Ted Melcer
Jay Walker
Brain Belnap
Michael Galarneau
Paula Konoske

Naval Health Research Center

Report No. 09-32

.

Naval Health Research Center
140 Sylvester Rd.
San Diego, California 92106-3521

Risk Factors Associated with

Diagnoses of Heterotopic Ossification in Recent Combat Amputees

Ted Melcer,[1] G. Jay Walker,[1] Brian Belnap,[2] Paula Konoske,[1] and Michael Galarneau[1]

[1]Medical Modeling, Simulation and Mission Support Department, Naval Health Research Center, San Diego, 140 Sylvester Rd., San Diego, CA 92106

[2]Comprehensive Combat and Complex Casualty Care, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134

Corresponding Author: Ted Melcer, Medical Modeling, Simulation and Mission Support Department, Naval Health Research Center, San Diego, 140 Sylvester Rd., San Diego, CA 92106. Telephone: (619) 553-8404, fax: (619) 553-0480, e-mail: ted.melcer@med.navy.mil

Abstract

Background: A significant complication impairing the rehabilitation of recent US combat amputees is heterotopic ossification, excess bone growth in residual limbs. This complication can develop in soft tissues of residual limbs many weeks after combat injury and interfere with prosthetic fitting and walking by causing skin breakdown and/or pain. Few studies have analyzed risk factors for heterotopic ossification among amputees injured in Operation Enduring Freedom and Operation Iraqi Freedom. The objective of the present research was to analyze factors associated with heterotopic ossification diagnosed during routine clinical encounters.

Methods: This was a retrospective analysis of heterotopic ossification, injury, and complication factors using diagnostic codes from the medical records of a comprehensive sample of combat amputees injured between 2001 and 2005 (n = 382). A list of 99 complications for recent combat amputees was designed by a trauma nurse and a combat casualty care physician.

Results: The results showed 18% of patients had heterotopic ossification diagnoses, which were significantly associated with increased injury severity, amputations in lower limbs versus upper limbs, amputations at higher levels (e.g., above elbow and above knee versus below elbow and below knee) and increased rates of several complications: osteomyelitis, infections, deep vessel thrombosis, and pulmonary embolism.

Conclusions: The present study extended previous research by showing significant associations between early complications and heterotopic ossification diagnoses. Medical record diagnoses were valid predictors of heterotopic ossification risk factors in a large sample. A diagnosis of heterotopic ossification occurred in approximately 1 in 5 patients, although this rate appeared low due to underreporting of heterotopic ossification early in Operation Enduring Freedom and Operation Iraqi Freedom.

Level of Evidence: Retrospective Level III. See Instructions to Authors for a complete description of levels of evidence.

Heterotopic ossification is a significant postinjury complication that can limit or delay the rehabilitation of combat amputees injured in Operation Enduring Freedom and Operation Iraqi Freedom[1-4]. This refers to excess bone growth that can develop in soft tissues of residual limbs many weeks after traumatic injury and interfere with prosthetic fitting and walking by causing skin breakdown and/or pain[1-4]. The development of acquired heterotopic ossification is believed to involve the following stages: (1) a traumatic injury, (2) a physiological signal from the locally injured tissue area, (3) the presence of mesenchymal cells in the injured area, and (4) an environment conducive to allowing further development of the heterotopic bone[5-12].

The individual variability in heterotopic ossification among combat amputees has not been studied extensively[1-4]. Potter and colleagues found that radiographs showed at least minor heterotopic ossification in 30% to 60% of amputees injured in Operation Enduring Freedom and Operation Iraqi Freedom[1]. However, the associated symptoms and patient diagnoses have had little study[1,2]. Some patients show no heterotopic ossification in radiographs, while some show radiographic heterotopic ossification but without symptoms or treatment. Most patients who have heterotopic ossification symptoms resolve them through prosthetic adjustments but some others require surgical excision[1,2].

Analysis of early predictors of heterotopic ossification can identify patients at risk and help to develop preventive strategies[1-4]. Initial studies of risk factors were based on large samples of patient radiographs[1,4]. Amputations, particularly those within the zone of blast injury, and high Injury Severity Scores predicted increased risk of excess bone growth following combat extremity injuries[1,4]. However, numerous postamputation complications[13-23], such as infections, phantom limb syndrome, deep vessel thrombosis, and pulmonary embolism have not received systematic study as possible risk factors[1,4].

Previous studies presented conflicting findings on wound complications as heterotopic ossification risk factors in combat amputees[1, 3]. One abstract (n = 195 patients) suggested that complications such as deep vessel thrombosis and wound infections increased heterotopic ossification risk[3], whereas a major study of combat amputees indicated heterotopic ossification was unrelated to complications[1]. Neither study showed when heterotopic ossification occurred postinjury relative to other complications.

Previous combat amputee samples also were limited by missing radiographs and/or to a specific medical facility[1,4], possibly inflating prevalence estimates because radiographs were not available for many patients. Provider diagnoses of postinjury complications such as heterotopic ossification are collected routinely and recorded longitudinally in medical databases, which also include systematic data on mechanism of injury and injury severity[24,25]. Provider diagnoses also may be more likely to indicate symptomatic heterotopic ossification than radiographs alone.

The present study was a retrospective analysis of a comprehensive sample of combat amputees injured between 2001 and 2005 to determine the rate and time course of heterotopic ossification and other complications during the first two years postinjury. Injury Severity Scores and complications [13-23] (e.g., infections, deep vessel thrombosis, osteomyelitis, pulmonary embolism) were compared between patients with and without a heterotopic ossification diagnosis to determine whether these factors might be related to later excess bone growth.

Method

Subjects

The present study followed institutional board approval. Subjects were U.S. warfighters in Operation Enduring Freedom or Operation Iraqi Freedom between 2001 and 2005 who suffered a combat injury leading to a major extremity amputation (excluding fingers and toes).

The methods for identification included a search of Navy-Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database [24] and Department of Defense medical databases for combat-related amputations. We identified 382 patients who represented most major limb amputees injured in Operation Enduring Freedom and Operation Iraqi Freedom combat amputees injured between 2001 and 2005[13].

Data Sources

Department of Defense medical data. Medical data were extracted from Standard Inpatient Data Records, Standard Ambulatory Data Records, and Health Care Service Records files via TRICARE Management Activity at Level 4 and 5 medical facilities, including International Classification of Diseases, Ninth Revision (ICD-9), diagnostic codes, surgical procedure codes, and disposition codes. These records are generated routinely for military personnel during inpatient and outpatient encounters, including diagnoses by credentialed providers at military treatment facilities and government-reimbursed private clinics.

Navy-Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database[24]. This database includes data from far-forward medical care at Navy-Marine Corps Levels 1B, 2, and 3, supplemented by data from Levels 4 and 5 military medical facilities including all military services. The Navy-Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database and the Joint Theater Trauma Registry[24,25] provided Injury Severity Scores.

Research Design

This was a retrospective review of existing medical records. Patients were followed for 24 months postinjury or until their medical records were no longer available in Department of Defense databases (usually due to military service discharge). Injuries that occurred during

Operation Enduring Freedom and Operation Iraqi Freedom through December 31, 2005, were included, which allowed at least 24 months of follow-up time for the present study. Outcome measures included standard diagnostic codes for complications such as infections recorded longitudinally in patient medical records.

The anatomical location of the amputation was the most recent level of amputation recorded in databases, including

a. below knee including foot amputation

b. above-knee amputation including through the knee and hip disarticulation

c. below elbow including wrist amputation

d. above-elbow amputation including shoulder disarticulation

e. bilateral amputation including upper, lower or upper and lower

Outcome Variables

The following variables were extracted from the databases:

1. Injury Severity Scores[26] were calculated for each patient.
2. Heterotopic ossification diagnostic codes. The following ICD-9 codes were used: 728.10, 728.12, 728.13.
3. Complications. A list of complications developed for the Navy-Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database was modified by a research trauma nurse and a combat casualty care physician. A final list of 99 complications was established for combat amputees. Complications were specific to residual limbs and general such as anemia or infections.
4. Traumatic brain injury. An ICD-9 diagnostic code in the following range within 30 days of injury was defined as traumatic brain injury[27]:

800.00-801.99 (fractures of the vault or base of the skull)

803.00-804.99 (other unqualified and multiple fractures of the skull)

850.00-854.10 (intracranial injury, including concussion, contusion, laceration, and hemorrhage)

Data Analysis

Percentages were based on the total number of patients. 15 percent of combat amputees lost more than one limb. However, diagnostic codes did not indicate whether heterotopic ossification occurred in one or both residual limbs. The Injury Severity Score and complications data were analyzed by comparing groups with and without heterotopic ossification diagnoses. Percentages were calculated for the entire follow-up period (i.e., 24 months or until study attrition) and within specific intervals during follow-up such as 3 months (quarters). There was some study attrition after the first year follow-up, usually due to discharge from service (i.e., some individuals' data were no longer available), and these individuals were not counted after the quarter in which they were discharged. Approximately 5% of the sample were lost to follow-up by 9 months after injury, and approximately 12% were lost by 12 months postinjury.

Source of Funding

Funding was provided by Office of the Assistant Secretary of Defense (Health Affairs), U.S. Army Medical Research and Materiel Command, Marine Corps Systems Command, and the Office of Naval Research.

Results

Demographics. A diagnosis of heterotopic ossification was not associated with age or service affiliation (only the Army and Marine Corps had substantial sample sizes for analysis). Virtually all injuries (96.8%) were caused by explosions or blasts, including improvised

explosive devices, rocket-propelled grenades, mortars, or landmines. Ninety-eight percent of the sample (375 of 382) had their first amputation within 1 month of combat injury.

Anatomical Location and Injury Severity Scores

Heterotopic ossification diagnoses occurred in approximately 1 in 5 patients (18.1%). Table I shows that lower extremity amputees had double the rate of heterotopic ossification diagnoses (20%) than upper extremity amputees (10%). The data for sublocations show that higher levels of amputation (above elbow, above knee) were associated with higher heterotopic ossification rates than lower levels (below elbow, below knee).

Overall, patients with heterotopic ossification diagnoses had significantly higher Injury Severity Scores than patients without this diagnosis (Table I). Most patients in all subgroups had serious injuries (Injury Severity Score > 9). Table II shows a direct relationship between higher injury severity groups and increasing percentage of heterotopic ossification cases. Patients with mild to moderate Injury Severity Scores had virtually no heterotopic ossification diagnoses, but heterotopic ossification occurred in 14% and 27% of patients with serious and severe Injury Severity Scores, respectively. This Injury Severity Score effect also was significant when single-limb amputees were analyzed separately.

Time Course of Heterotopic Ossification Postinjury

Table III shows that 78% of new heterotopic ossification cases (54 of 69) occurred within 9 months postinjury. New cases declined sharply thereafter, with only eight additional new cases during the second year.

Traumatic Brain Injury

There was a marginal association between traumatic brain injury and heterotopic ossification diagnoses ($p < .07$), with a slightly higher percentage of traumatic brain injury

patients who had heterotopic ossification (30%) than those who did not develop heterotopic ossification (20%).

Complications

Table IV shows the most frequently diagnosed complications grouped by patients who had a heterotopic ossification diagnosis (n = 69) versus those without this diagnosis (n = 313). The rates of all complications were numerically higher for heterotopic ossification than non-heterotopic ossification patients, although the overall difference was not significant. However, phantom limb syndrome and infections, such as osteomyelitis and chronic infection of the amputation stump, had significantly higher rates among heterotopic ossification patients. Both deep vessel thrombosis and pulmonary embolism were more than twice as likely among heterotopic ossification patients than those without heterotopic ossification.

Table V shows complications categorized as infections, stump complications, and other issues. Data are grouped by patients who had a heterotopic ossification diagnosis at some point after injury (n = 69) versus those without this diagnosis (n = 313). The first 30 days' time period after injury is critical to recovery and is presented separately from the second 60 days. Subsequent intervals are quarters of 90 days. Those complications, which were shown in Table IV to have significantly higher overall rates in heterotopic ossification patients (phantom limb syndrome, osteomyelitis, chronic infection, deep vessel thrombosis, pulmonary embolism), also showed numerically higher rates during the first 9 months after injury. These differences appear earlier for deep vessel thrombosis and pulmonary embolism (first 30 days) than for osteomyelitis, chronic infection, and phantom limb syndrome (between 3 and 9 months). Septicemia was one infection that did show a numerically higher rate among heterotopic

ossification than non-heterotopic ossification patients during the first 30 days after injury, but the overall effect across all intervals was only marginally significant ($p < .10$).

Discussion

The present study is one of the first to show evidence of associations between heterotopic ossification and early wound complications, such as osteomyelitis, pulmonary embolism, deep vessel thrombosis, and phantom limb syndrome[1,3,4]. A diagnosis of heterotopic ossification occurred in approximately 1 in 5 patients and also was associated with increased injury severity, lower limb amputation, and higher levels of amputation. Medical record diagnoses were valid measures to identify factors associated with heterotopic ossification such as injury severity and lower limb amputations, replicating similar results from previous studies, which used radiographic methods[4]. The use of routine medical diagnoses also allowed identification of heterotopic ossification and associated risk factors in a comprehensive sample of recent combat amputees. A previous study sample of combat amputees was limited by missing patient radiographs following injury, which led to exclusion of approximately 40% of relevant patients[1].

The present results extend previous research by showing systematic evidence of associations between early wound complications and heterotopic ossification diagnoses[1]. This finding conflicts with one major previous study of heterotopic ossification in recent combat amputees that reported no associations between early competitions and heterotopic ossification[1]. However, the present results are consistent with a subsequent abstract that reported that heterotopic ossification status was associated with wound infections and deep vessel thrombosis [3]. In the present study, it was possible to identify and follow specific types of complications (e.g., osteomyelitis, deep vessel thrombosis) based on diagnostic codes recorded longitudinally in each patient's medical record.

The increased rates of various complications may be independent effects of severe injury and not directly related to heterotopic ossification[4]. Alternatively, complications may be involved in the physiological development of heterotopic ossification. However, deep vessel thrombosis and some infections are differential diagnoses for a swollen lower extremity along with heterotopic ossification[6,28]. It is possible that these complications initially may be confused with actual heterotopic ossification cases.

The main limitation of the present study was that the diagnosis rate of 18% was low relative to heterotopic ossification rates of 30% to 60% in radiographs reported in recent reports[1,4], probably due to methodological differences and/or underreporting. The present study based percentages on number of patients versus number of limbs or wounds[1,4]. Also, Potter and co-authors acknowledged their rates probably were inflated because nearly half of their sample (143 of 330) was excluded due to missing radiographs[1]. Providers generally order radiographs for symptomatic patients. When they included all 330 patients (including those without radiographs), Potter indicated 36% of all 330 patients showed at least mild radiographic evidence of heterotopic ossification (assuming no heterotopic ossification in all of the limbs with missing radiographs). Moreover, a positive radiograph does not always predict patient symptoms. An unpublished manuscript by the present authors based on a small case series of recent combat amputees showed 5 of 15 patients showed at least moderate heterotopic ossification[1] in their radiographs but reported no symptoms or treatments such as pain or prosthetic adjustments[29]. While these latter results were based on a small sample, they suggest further reduction from the estimated 36% in a previous study[1].

The diagnosis rate in the present study also was underestimated probably due to underreporting early in Operation Enduring Freedom and Operation Iraqi Freedom, since

heterotopic ossification was unexpected[1, 2]. Specifically, the present study showed a heterotopic ossification diagnosis rate of 8% of patients through August 2004, versus 26% thereafter through the end of 2005. Similarly, another study showed that the heterotopic ossification incidence rate among U.S. military battle and nonbattle injuries was relatively flat between 2002 and 2003, with an increase of 60% to 65% between 2003 and 2004[30]. A recent report indicated heterotopic ossification in intact limbs[4] and demonstrated increased heterotopic ossification risk in residual limbs of combat amputees. Although these data suggest increased awareness of combat-related heterotopic ossification, providers should remain vigilant for this complication following combat-related blast injuries.

Acknowledgments

Report No. 09-32 was supported by the Office of Naval Research, Arlington, VA, under Work Unit No. 60332. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government. Approved for public release; distribution is unlimited. Human subjects participated in this study after giving their free and informed consent. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (protocol NHRC.2007.0016).

References

1. Potter BK, Burns TC, Lacap AP, Granville RR, Gajewski D. Heterotopic ossification following traumatic and combat-related amputations: prevalence, risk factors, and preliminary results of excision. J Bone Joint Surg Am. 2007;89-A(3):476-86.

2. Potter BK, Burns TC, Lacap AP, Granville RR, Gajewski D. Heterotopic ossification in the residual limbs of traumatic and combat-related amputees. Journal of the American Academy of Orthopedic Surgeons. 2006;14(10):S191-S7.

3. Greenwell GT, Pasquina P, Luu V, Gajewski D, Scoville C, Doukas W. Incidence of heterotopic ossification in the combat amputee. Arch Phys Med Rehabil. 2006;87:E20.

4. Forsberg JA, Pepek JM, Wagner S, Wilson K, Flint J, Andersen RC, et al. Heterotopic ossification and high-energy wartime extremity injuries: prevalence and risk factors. J Bone Joint Surg Am. 2009; 91:1084-91.

5. Martínez FJA, Mateau JMM, Ferrero VT. The role of radiotherapy for prevention of heterotopic ossification after major hip surgery. Clin Transl Oncol. 2007;9:28-31.

6. Cullen N, Bayley M, Bayona N, Hilditch M, Aubut J. Management of heterotopic ossification and venous thromboembolism following acquired brain injury. Brain Inj. 2007;21:215-30.

7. Balboni TA, Gobezie R, Mamon HJ. Heterotopic ossification: pathophysiology clinical features and the role of radiotherapy for prophylaxis. Int J Radiat Oncol Biol Phys. 2006;65:1289-99.

8. McCarthy EF, Sundaram M. Heterotopic ossification: a review. Skeletal Radiol. 2005;34:609-19.

9. Kaplan FS, Glaser DL, Hebela N, Shore EM. (2004) Heterotopic ossification. Journal of the American Academy of Orthopedic Surgeons. 2004;12:116-25.

10. Hunt JL, Arnoldo BD, Kowalske K, Helm P, Purdue GF. (2006) Heterotopic ossification revisited: a 21-year surgical experience. J Burn Care Research. 2006; 27:535-40.

11. Dudek NL, DeHaan MN, Marks MB. Bone overgrowth of the adult traumatic amputee American Journal of Medical Rehabilitation. 2003;82:897-900.

12. Warmoth JE, Riegel B, McFall TL, Pugh G, Alvarez L, Melton D.M., Shelton A.D. . Heterotopic ossification associated with traumatic amputation. Journal of Prosthetics and Orthotics. 1997;9:33-7.

13. Potter BK, Scoville CR. Amputation is not isolated: an overview of the US Army amputee patient care program and associated amputee injuries. Journal of the American Academy of Orthopedic Surgeons. 2006;14:S188-90.

14. Covey D, Aaron RK, Born CT, Calhoun JH, Einhorn TA, Hayda RA, Levin LS, Mazurek MT, Murray CK, Powell ET, Schwarz EM, Wenke JC. Orthopedic war injuries: from combat casualty to definitive treatment: a current review of clinical advances basic science and research opportunities. Instr Course Lect. 2008;57:65-86.

15. Johnson BA, Carmack D, Neary M, Tenuta J. Operation Iraqi Freedom: the Landstuhl Regional Medical Center experience. J Foot Ankle Surg. 2005;44:177-83.

16. Petersen K, Riddle MS, Danko JR, Blazes DL, Hayden R, Tasker SA, Dunne JR. Trauma-related infections in battlefield casualties from Iraq. Ann Surg. 2007;245:803-11.

17. Owens BD, Kragh MD, Macaitis JF, Svoboda J, Wenke JC. Characterization of extremity wounds in Operation Iraqi Freedom and Operation Enduring Freedom. J Orthop Trauma. 2007;21:254-7.

18. Murray CK, Hsu JR, Solomkin JS, Keeling JJ, Andersen RC, Ficke JR, Calhoun JH. Prevention and management of infections associated with combat related extremity injuries: Clinical Practice Guidelines Consensus Conference. J Trauma. 2008;64 Suppl 3:S239-51.

19. Anderson RC, Frisch M, Farber GL, Hayda RA. Definitive treatment of combat casualties at military medical centers. Journal of the American Academy of Orthopedic Surgeons. 2006;14:S24-31.

20. Lin DL, Kirk KL, Murphy KP, McHale KA, Doukas W. Evaluation of orthopaedic injuries in operation enduring freedom. J Orthop Trauma. 2004;18Suppl. 8:S48-S53.

21. Yun HC, Branstetter JG, Murray CK. Osteomyelitis and military personnel wounded in Iraq and Afghanistan. J Trauma. 2008;64:S163-8.

22. Ketz AK. Pain management in the traumatic amputee. Crit Care Nurs Clin North Am. 2008;20:51-7.

23. Franklin A, Pasquina PF, Luu V, Scoville C, Doukas W. The incidence of deep venous thrombosis and pulmonary embolism in the combat amputee. Arch Phys Med Rehabil. 2006;87:E30.

24. Galarneau MR, Hancock WC, Konoske P, Melcer T, Vickers RR, Walker J, Zouris JM. The Navy-Marine Corps Combat Trauma Registry. Mil Med. 2006;171:691-7.

25. Eastridge BJ, Jenkins D, Flaherty S, Schiller H, Holcomb JB. Trauma system development in a theater of war: experiences from Operation Iraqi Freedom and Operation Enduring Freedom. J Trauma. 2006;61:1366-72.

26. Champion HR. Trauma scoring. Scand J Surg. 2002;91:12-22.

27. Centers for Disease Control and Prevention. Traumatic brain injury in the United States: a report to Congress. http://www.cdc.gov/ncipc/tbi/tbi_congress/05_references_appendix.pdf. Accessed 2008 Oct. 15.

28. Bradleigh LH, Perkash A, Linder SH, Sullivan GH, Bhatt HK, Perkash I. Deep venous thrombosis associated with heterotopic ossification. Arch Phys Med Rehabil. 1992;73:293-4.

29. Melcer T, Belnap B, Walker GJ, Konoske PJ, Galarneau MR. Heterotopic ossification recent combat amputees: six case histories and results from a small patient series. Submitted for publication.

30. Jefferies VN. Heterotopic ossification: U.S. Armed Forces 2002-2007. Medical Surveillance Monthly Report. 2007;14:7-9.

TABLE I. Heterotopic Ossification (HO) Diagnoses and Injury Severity Scores Among Combat Amputees (N = 382) by Anatomical Location of Amputation

Location	No.	Mean Injury Severity Score	Median Injury Severity Score	Sublocation	No. HO/Total	%
Upper extremity				Upper extremity		
HO diagnosis	9 (10%)	19.8	17	Above elbow	5/37	14%‡
No diagnosis	82 (90%)	17.6	17	Below elbow	2/49	4%
				Bilateral	2/5	--
Lower extremity				Lower extremity		
HO diagnosis	55 (20%)*	17.9	17	Above knee	24/92	26%‡
No diagnosis	223 (80%)	13.7	10	Below knee	18/143	13%
				Bilateral	13/43	30%
Upper & lower						
HO diagnosis	4	23.0	21			
No diagnosis	7	23.2	18			
Not recorded						
HO diagnosis	1	25.0				
No diagnosis	1	11.0				
Total sample						
HO diagnosis	69 (18%)	18.5†	17			
No diagnosis	313 (82%)	14.9	12			

*Upper/lower extremity by heterotopic ossification diagnosis/no diagnosis, $p < .05$, chi-square test.

†Mean Injury Severity Score by heterotopic ossification diagnosis/no diagnosis groups, $p < .01$, independent groups t test.

‡Higher level of amputation (above elbow/knee vs. below elbow/knee) by heterotopic ossification diagnosis/no diagnosis, $p < .05$, chi-square test.

TABLE II. Heterotopic Ossification as a Function of Moderate Serious and Severe Injury Groupings in Combat Amputees

	Injury Severity Groups		
HO Status	Moderate (Injury Severity Score = 4-8)	Serious (Injury Severity Score = 9-15)	Severe (Injury Severity Score >15)
HO diagnosis	2% (n = 1)	14% (n = 22)	27% (n = 46)
No diagnosis	98% (n = 46)	86% (n = 140)	73% (n = 127)

Significant association between Injury Severity Score grouping and heterotopic ossification status, $p < .01$, chi-square test.

TABLE III. Frequency of New-Onset Diagnoses of Heterotopic Ossification* by Time Since Injury

	Time Since Injury				
	First 30 Days	30-90 Days	3-6 Months	6-9 Months	9-12 Months
New heterotopic ossification cases (no.)	9	9	20	16	7
Amputees still active (no.)	382	376	372	361	326
New cases	2.4%	2.4%	5.4%	4.4%	2.1%

*Eight total heterotopic ossification cases between 12 and 24 months after injury.

TABLE IV. Most Common Complications Among Combat Amputees by Heterotopic Ossification Status

Complication	No./Total Heterotopic Ossification	No./Total Non-Heterotopic Ossification
Phantom limb syndrome	47/69 (68%)	165/313 (53%)*
Anemia	35/69 (51%)	134/313 (43%)
Bacterial infection	24/69 (35%)	78/313 (25%)
Postoperative infection	20/69 (29%)	82/313 (26%)
Osteomyelitis	22/69 (32%)	62/313 (20%)*
Cellulitis	18/69 (26%)	51/313 (16%)
Amputation stump complications	17/69 (25%)	49/313 (16%)
Chronic infection amputation stump	18/69 (26%)	38/313 (12%)†
Deep vessel thrombosis	13/69 (19%)	23/313 (7%)†
Pulmonary embolism	11/69 (16%)	16/313 (5%)†
Pneumonia	10/69 (15%)	37/313 (12%)
Infection/inflammatory due to device	9/69 (13%)	35/313 (11%)
Nonhealing wound	10/69 (15%)	32/313 (10%)
Septicemia	12/69 (17%)	30/313 (10%)

*$p < .05$; †$p < .01$.

Overall rate of infection: heterotopic ossification = 71% (49 of 69) vs. non-heterotopic ossification 54% (170 of 313).*

TABLE V. Complications by Heterotopic Ossification* (HO) Status During the First Year Postinjury

	Time Since Injury				
Complication	Within 30 Days	1-3 Months	3-6 Months	6-9 Months	9-12 Months
Infections					
Septicemia					
HO	15.9%	1.4%	1.4%	0.0%	0.0%
Non-HO	8.3%	2.0%	1.0%	0.0%	0.0%
Bacterial infection					
HO	13.0%	2.9%	14.5%	7.2%	3.0%
Non-HO	17.6%	4.9%	2.0%	2.4%	1.9%
Postoperative infection					
HO	14.5%	5.8%	4.3%	7.2%	4.5%
Non-HO	16.3%	8.8%	4.0%	2.1%	2.7%
Osteomyelitis					
HO	8.7%	13.0%	11.6%	7.2%	3.0%
Non-HO	10.8%	8.1%	4.3%	3.1%	3.9%
Chronic infection					
HO	7.2%	2.9%	11.6%	5.8%	3.0%
Non-HO	6.1%	2.0%	1.3%	1.0%	2.3%
Infection/inflammatory due to device					
HO	2.9%	5.8%	2.9%	1.4%	0.0%
Non-HO	7.0%	2.0%	3.0%	2.4%	1.2%
Stump complications					
Phantom limb syndrome					
HO	29.0%	36.2%	29.0%	10.1%	11.9%
Non-HO	24.3%	23.5%	17.5%	11.6%	8.1%
Amputation stump					
HO	2.9%	2.9%	7.2%	4.3%	7.5%
Non-HO	2.9%	4.2%	5.6%	3.4%	3.1%
Other complications					
Nonhealing wound					
HO	8.7%	5.8%	5.8%	1.4%	0.0%
Non-HO	5.4%	4.9%	2.3%	0.7%	0.8%
Deep vessel thrombosis					
HO	11.6%	5.8%	2.9%	1.4%	0.0%
Non-HO	4.5%	2.0%	1.7%	0.3%	0.0%

Pulmonary embolism					
HO	13.0%	5.8%	5.8%	4.3%	0.0%
Non-HO	3.8%	3.3%	2.0%	1.4%	0.0%

*Heterotopic ossification: n = 69; non-heterotopic ossification: n = 313.

REPORT DOCUMENTATION PAGE

1. Report Date (DD MM YY)
07 22 09

2. Report Type
Journal submission

3. DATES COVERED (from - to)
September 2008 to March 2009

4. TITLE AND SUBTITLE
Risk Factors Associated with Diagnoses of Heterotopic Ossification in Recent Combat Amputees

5a. Contract Number:
5b. Grant Number:
5c. Program Element:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number: 60332

6. AUTHORS
Ted Melcer, Jay Walker, Brian Belnap, Michael Galarneau, Paula Konoske

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Commanding Officer
Naval Health Research Center
140 Sylvester Rd.
San Diego, CA 92106

8. PERFORMING ORGANIZATION REPORT NUMBER
09-32

8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)
Commanding Officer
Naval Medical Research Center
503 Robert Grant Ave
Silver Spring, MD 20910-7500

Commander
Navy Medicine Support Command
P.O. Box 140
Jacksonville, FL 32213-0140

10. Sponsor/Monitor's Acronyms(s)
NMRC/NMSC

11. Sponsor/Monitor's Report Number(s)

12 DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES
This is a peer-reviewed journal submission. Do not cite, quote, or release until publication.

14. ABSTRACT (maximum 200 words)

A significant complication impairing the rehabilitation of recent combat amputees is heterotopic ossification (HO), excess bone growth in residual limbs. Few studies have analyzed risk factors for HO among amputees injured in Operation Enduring Freedom and Operation Iraqi Freedom. The present research investigated injury factors and complications associated with HO diagnoses during routine clinical encounters by retrospective review of medical records of combat amputees injured between 2001 and 2005 (n = 382). The results showed 18% of patients had HO diagnoses, which were significantly associated with increased injury severity, amputations at higher levels (e.g., above elbow and above knee versus below elbow and below knee) and in lower limbs, and increased rates of several complications: osteomyelitis, infections, deep vessel thrombosis, and pulmonary embolism. The present study extended previous research by showing significant associations between early complications and HO diagnoses. Medical record diagnoses were valid predictors of HO risk factors in a large sample. A diagnosis of HO occurred in approximately 1 in 5 patients, although this rate appeared low due to underreporting early in Operation Enduring Freedom and Operation Iraqi Freedom.

14. SUBJECT TERMS
combat amputee, heterotopic ossification, case histories, rehabilitation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	18a. NAME OF RESPONSIBLE PERSON
a. REPORT	b.ABSTRACT	b. THIS PAGE			Commanding Officer
UNCL	UNCL	UNCL	UNCL	24	18b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39-18